Using Computational Tools to Inform HIV Vaccine Design

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The World Health Organization estimates that 60 million people worldwide have been infected with the human immunodeficiency virus since it was first identified. Although treatments are available for managing this disease for some period of time, they are expensive, can cause debilitating side effects, and condemn the patient to a life-long regimen. Drug-resistant HIV is beginning to be transmitted, and may compromise our ability to treat the disease. Safe, practical, and effective vaccines are urgently needed, but they remain elusive.

The immune system evolved to recognize foreign antigens and eliminate them using antibodies and cell-mediated response. The interactions are very specific and, once established, HIV manages to evade this response by mutating fast. Vaccines aim at training the immune system by presenting epitopes similar to those presented by HIV particles or HIV infected cells, and prepare the body for future infections. But, since the diversity of circulating HIV forms is large (see Fig. 1), it is not clear as to which epitopes the vaccine should expose the immune system. Much of the current research in vaccine design is heuristic and empirical. The central challenge is to design vaccines that stimulate immune response broad enough to neutralize a wide range of viruses. All candidate HIV vaccines currently in clinical development are derived from natural isolates, and the strain used is often based on availability. The first two human trials using these methods did elicit antibodies, but they were not cross-reactive enough to prevent infection.

A large amount of data is, however, available in the Los Alamos HIV database about the genetic sequence of the virus, and immunological epitopes it presents. This data can be used to study the evolution of the viral genome and these epitopes. One can therefore hope to locate parts of the genome that have stayed relatively conserved throughout its evolution and try to locate epitopes in this region. Alternatively, one can try to design peptides containing epitopes presented by diverse HIV subtypes. The vaccine strain can then be designed to express these epitope-rich structures.

As a first step, our team used this data to design an artificial "central" protein which is less distant, on average, from the circulating strains than they are from each other. The

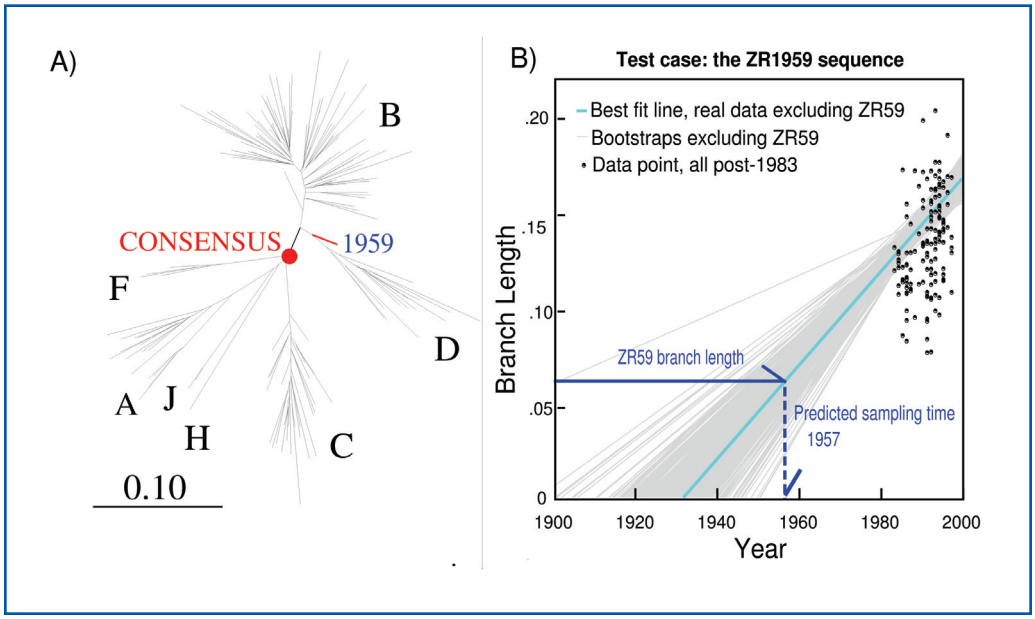

Figure 1—
Genetic diversity of HIV-1 M group viruses and how it is increasing through time.

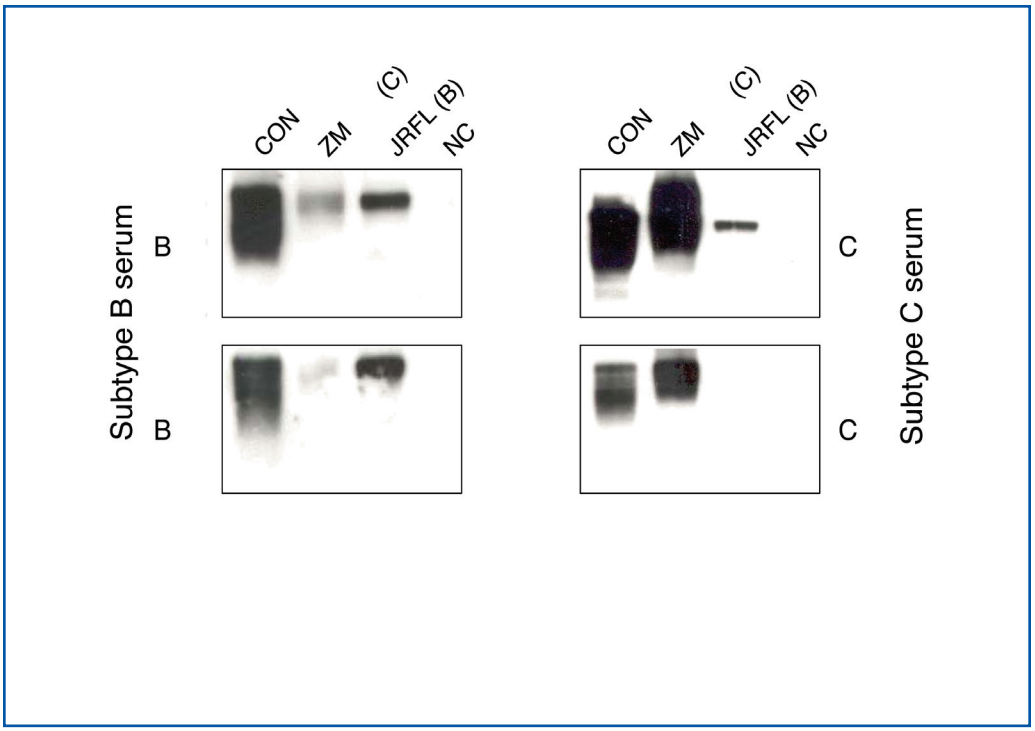

Figure 2—
Broad cross-clade reactivity of the M group consensus gp120 with patient sera of different clades in a Western blot assay. The central (CON6) construct shows activity comparable to subtype B (JRFL) and C (96ZM651) isolates against sera of the same subtype, and markedly more than that against sera of the dissimilar subtype.

resulting protein folded properly, was weakly functional, and induced antibodies that were cross reactive (see Fig. 2). We now plan to test this first-generation vaccine in animal trials, and try to improve it using data from early infections.